(FILE 'HOME' ENTERED AT 20:03:04 ON 20 FEB 2001)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS, MEDICONF'
ENTERED AT 20:03:11 ON 20 FEB 2001

```
L1        105404 S P53
L2            36 S L1 AND (SINGLE CHAIN ANTIBOD?)
L3            20 DUP REM L2 (16 DUPLICATES REMOVED)
L4            20 SORT L3 PY
L5          2875 S L1 AND (GENE THERAPY)
L6           565 S L5 AND MUTANT
L7            64 S L6 AND SINGLE
L8             7 S L6 AND (SINGLE CHAIN)
L9             7 S L6 AND (SFV OR SINGLE CHAIN)
L10            2 DUP REM L9 (5 DUPLICATES REMOVED)
```

=> d ti so au ab l10 1-2

L10 ANSWER 1 OF 2 MEDLINE DUPLICATE 1

TI A tumor specific **single chain** antibody dependent gene expression system.

SO ONCOGENE, (1999 Jan 14) 18 (2) 559-64.
Journal code: ONC. ISSN: 0950-9232.

AU Mary M N; Venot C; Caron de Fromentel C; Debussche L; Conseiller E; Cochet O; Gruel N; Teillaud J L; Schweighoffer F; Tocque B; Bracco L

AB The design of conditional gene expression systems restricted to given tissues or cellular types is an important issue of **gene therapy**. Systems based on the targeting of molecules characteristic of the pathological state of tissues would be of interest. We have developed a synthetic transcription factor by fusing a **single chain** antibody (scFv) directed against **p53** with the bacterial tetracycline repressor as a DNA binding domain. This hybrid protein binds to **p53** and can interact with a synthetic promoter containing tetracycline-operator sequences. Gene expression can now be specifically achieved in tumor cells harboring an endogenous **mutant p53** but not in a wild-type **p53** containing tumor cell line or in a non-transformed cell line. Thus, a functional transactivator centered on **single chain** antibodies can be expressed intracellularly and induce gene expression in a scFv-mediated specific manner. This novel class of transcriptional transactivators could be referred as 'trabodies' for transcription-activating-antibodies. The trabodies technology could be useful to any cell type in which a disease related protein could be the target of specific antibodies.

L10 ANSWER 2 OF 2 SCISEARCH COPYRIGHT 2001 ISI (R) DUPLICATE 2

TI Restoration of transcriptional activity of **p53 mutants** in human tumour cells by intracellular expression of anti-**p53 single chain** Fv fragments

SO ONCOGENE, (14 JAN 1999) Vol. 18, No. 2, pp. 551-557.
Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND.
ISSN: 0950-9232.

AU deFromentel C C (Reprint); Gruel N; Venot C; Debussche L; Conseiller E; Dureuil C; Teillaud J L; Tocque B; Bracco L

AB We report here the production and the properties of **single chain** Fv fragments (scFvs) derived from the anti-**p53** monoclonal antibodies PAb421 and 11D3, 11D3 is a newly generated monoclonal antibody which exhibits properties very comparable to those of PAb421, The scFvs PAb421 and 11D3 are able to stably associate with **p53** and to restore the DNA binding activity of some **p53 mutants** in vitro. When expressed in **p53**(-/-) human tumour cells, the scFv421 is essentially localized in the cytoplasm in the absence of **p53**, and in the nucleus when exogenous **p53** is present, Thus, **p53** is also able to stably associate with an anti-**p53** scFv in cells. Cotransfection of **p53**(-/-) human tumour cells with expression vectors encoding the His273 **p53 mutant** and either scFv leads to restoration of the **p53 mutant** deficient transcriptional activity. These data demonstrate that, in human tumour cells, these scFvs are able to restore a function essential for the tumour suppressor activity of **p53** and may represent a novel class of molecules for **p53**-based cancer therapy.

L4 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2001 ACS

TI Anti-p53 **single-chain antibody** fragments and their uses

SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2

IN Bracco, Laurent; Debussche, Laurent

AB The invention concerns **single-chain antibodies** directed against the **p53** protein, capable of being expressed in tumor cells, capable of restoring a DNA binding in vitro and a transcription activator function in vivo. The invention also concerns nucleic acids coding for these mols., the vectors contg. them and their uses.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9818825	A1	19980507	WO 1997-FR1921	19971027
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GH, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
FR 2755144	A1	19980430	FR 1996-13176	19961029
FR 2755144	B1	19981127		
AU 9749520	A1	19980522	AU 1997-49520	19971027
EP 941252	A1	19990915	EP 1997-912262	19971027
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI				
BR 9712575	A	19991019	BR 1997-12575	19971027
NO 9901729	A	19990413	NO 1999-1729	19990413

L4 ANSWER 4 OF 20 MEDLINE
TI Characterization of scFv-421, a **single-chain antibody** targeted to **p53**.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1997 Jan 13) 230 (2) 242-6.
Journal code: 9Y8. ISSN: 0006-291X.
AU Jannot C B; Hynes N E
AB A gene encoding a **single-chain antibody** (scFv) which specifically binds the tumor suppressor protein **p53** has been constructed from RNA of hybridoma cells producing Pab 421. scFv-421 which was expressed and purified from bacteria specifically binds **p53**. scFv-421, as well as the previously described scFv-FRP5 and -R1R (1), were expressed intracellularly in mammalian cells and targeted to different subcellular locations, including the nucleus, cytoplasm, and endoplasmic reticulum (ER). High levels of all ER targeted scFv proteins, but not nuclear or cytoplasmic targeted proteins, were found in transfected COS-1 cells. In an attempt to stabilize the proteins, sequences encoding the mouse immunoglobin CK constant domain were added to each scFv construct. This led to a moderate increase in the cytoplasmic expression of scFv-FRP5.

L4 ANSWER 7 OF 20 MEDLINE

TI Characterization of a new intrabody directed against the N-terminal region of human **p53**.

SO ONCOGENE, (1998 Nov 12) 17 (19) 2445-56.
Journal code: ONC. ISSN: 0950-9232.

AU Cohen P A; Mani J C; Lane D P

AB Genes encoding the rearranged immunoglobulin heavy and light chain variable regions of DO-1, a monoclonal antibody directed against human **p53**, have been used to construct a **single-chain antibody**. DO-1 recognizes an N-terminal epitope in the region involved in the transactivation function of **p53** and the binding of Mdm2. The DO-1 single chain scFv expressed in the periplasm of E. coli or at the surface of the filamentous phage M13 retained the immunological specificity and affinity of the full length antibody. Furthermore, the DO-1 recombinant antibody was able to inhibit the in vitro binding of Hdm2, and was shown to be a powerful protecting agent of **p53**'s DNA binding activity at 37 degrees C. The DO-1 **single-chain antibody** has been used to construct single-chain intracellular antibodies (intrabodies) for expression in the cytoplasm and the nucleus of mammalian cells. These anti-**p53** intrabodies were additionally modified by addition of a Ckappa domain to increase cytoplasmic and nuclear stability. Here we show that expression of the DO-1 **single-chain antibody** in the H1299 cell line results in an inhibition of **p53**'s transactivation function. The DO-1 intrabody is a useful tool to study those functions of **p53** driven by the N-terminal region of the protein.

L4 ANSWER 12 OF 20 MEDLINE
TI A tumor specific **single chain antibody** dependent gene expression system.
SO ONCOGENE, (1999 Jan 14) 18 (2) 559-64.
Journal code: ONC. ISSN: 0950-9232.
AU Mary M N; Venot C; Caron de Fromentel C; Debussche L; Conseiller E; Cochet O; Gruel N; Teillaud J L; Schweighoffer F; Tocque B; Bracco L
AB The design of conditional gene expression systems restricted to given tissues or cellular types is an important issue of gene therapy. Systems based on the targeting of molecules characteristic of the pathological state of tissues would be of interest. We have developed a synthetic transcription factor by fusing a **single chain antibody** (scFv) directed against **p53** with the bacterial tetracycline repressor as a DNA binding domain. This hybrid protein binds to **p53** and can interact with a synthetic promoter containing tetracycline-operator sequences. Gene expression can now be specifically achieved in tumor cells harboring an endogenous mutant **p53** but not in a wild-type **p53** containing tumor cell line or in a non-transformed cell line. Thus, a functional transactivator centered on **single chain antibodies** can be expressed intracellularly and induce gene expression in a scFv-mediated specific manner. This novel class of transcriptional transactivators could be referred as 'trabodies' for transcription-activating-antibodies. The trabodies technology could be useful to any cell type in which a disease related protein could be the target of specific antibodies.

L4 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2001 ACS

TI Restoration of transcriptional activity of **p53** mutants in human tumor cells by intracellular expression of anti-**p53** single chain Fv fragments

SO Oncogene (1999), 18(2), 551-557
CODEN: ONCNES; ISSN: 0950-9232

AU De Fromentel, Claude Caron; Gruel, Nadege; Venot, Corinne; Debussche, Laurent; Conseiller, Emmanuel; Dureuil, Christine; Teillaud, Jean-Luc; Tocque, Bruno; Bracco, Laurent

AB The authors report here the prodn. and the properties of single chain Fv fragments (scFvs) derived from the anti-**p53** monoclonal antibodies PAb421 and 11D3. 11D3 is a newly generated monoclonal antibody which exhibits properties very comparable to those of PAb421. The scFvs PAb421 and 11D3 are able to stably assoc. with **p53** and to restore the DNA binding activity of some **p53** mutants in vitro. When expressed in **p53**-/- human tumor cells, the scFv421 is essentially localized in the cytoplasm in the absence of **p53**, and in the nucleus when exogenous **p53** is present. Thus, **p53** is also able to stably assoc. with an anti-**p53** scFv in cells. Contransfection of **p53**-/- human tumor cells with expression vectors encoding the His273 **p53** mutant and either scFv leads to restoration of the **p53** mutant deficient transcriptional activity. These data demonstrate that, in human tumor cells, these scFvs are able to restore a function essential for the tumor suppressor activity of **p53** and may represent a novel class of mols. for **p53**-based cancer therapy.

L4 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2001 ACS
TI Antibody fragment-targeted immunoliposomes for systemic gene delivery
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
IN Xu, Liang; Huang, Cheng-Cheng; Alexander, William; Tang, Wenhua; Chang, Esther H.
AB Nucleic acid-immunoliposome compns. useful as therapeutic agents are disclosed. These compns. preferably comprise (i) cationic liposomes, (ii) a **single chain antibody** fragment which binds to a transferrin receptor, and (iii) a nucleic acid encoding a wild type **p53**. These compns. target cells which express transferrin receptors, e.g., cancer cells. These compns. can be used therapeutically to treat persons or animals who have cancer, e.g., head and neck cancer, breast cancer or prostate cancer.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000050008	A2	20000831	WO 2000-US4392	20000222
WO 2000050008	A3	20001221		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

=> DIS HIS

(FILE 'HOME' ENTERED AT 14:43:01 ON 06 JUN 2000)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS, CANCERLIT, USPATFULL' ENTERED AT 14:43:53 ON 06 JUN 2000

```
L1          4495 S SINGLE CHAIN ANTIBOD?
L2            45 S P53 PROTEIN AND L1
L3            42 DUP REM L2 (3 DUPLICATES REMOVED)
L4            72 S MUTATED P53 PROTEIN AND TREAT?
L5            22 S L4 AND PY<1996
L6            12 DUP REM L5 (10 DUPLICATES REMOVED)
L7             0 S L1 AND L4
L8             0 S L1 AND TREAT? MUTATED P53 CANCER
L9             0 S MODIFY? MUTATED P53 CONFORMATION AND L1
L10            0 S MUTATED P53 PROTEIN AND P53H273
L11            0 S MUTATED P53 PROTEIN AND P53W248
L12            0 S MUTATED P53 PROTEIN AND P53G281
L13           58 S MUTATED P53 PROTEIN AND TUMOR CELL#
L14           20 S L13 AND PY<1996
L15           11 DUP REM L14 (9 DUPLICATES REMOVED)
L16            0 S SINGLE CHAIN ANTIBOD? BIND MUTATED P53 PROTEIN
L17            6 S SINGLE CHAIN ANTIBOD? AND MUTATED P53
L18            6 DUP REM L17 (0 DUPLICATES REMOVED)
```